

## Clinical Investigation and Reports

# Efficacy and Safety of Ezetimibe Coadministered With Atorvastatin or Simvastatin in Patients With Homozygous Familial Hypercholesterolemia



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**Background**—Patients with homozygous familial hypercholesterolemia (HoFH) have a high incidence of cardiovascular morbidity and mortality from premature atherosclerosis, and the efficacy of pharmacological therapy has been limited. We evaluated the efficacy, safety, and tolerability of ezetimibe, a novel cholesterol absorption inhibitor, in a multicenter, double-blind, randomized trial of HoFH patients receiving atorvastatin or simvastatin.

**Methods and Results**—Fifty patients with a diagnosis of HoFH on the National Cholesterol Education Program Step I or stricter diet and taking open-label atorvastatin 40 mg/d or simvastatin 40 mg/d (statin-40) with (n=25) or without (n=25) concomitant LDL apheresis were randomized to 1 of 3 double-blind treatments: atorvastatin or simvastatin 80 mg/d (statin-80, n=17); ezetimibe 10 mg/d plus atorvastatin or simvastatin 40 mg/d (n=16); or ezetimibe 10 mg/d plus atorvastatin or simvastatin 80 mg/d (n=17) for 12 weeks. The primary end point was mean percentage change in LDL cholesterol (LDL-C) from statin-40 baseline to the end point for patients receiving statins alone (statin-80) versus patients receiving ezetimibe plus atorvastatin or simvastatin at either dose (ezetimibe plus statin-40/80). Ezetimibe plus statin-40/80 significantly reduced LDL-C levels compared with statin-80 (−20.7% versus −6.7%,  $P=0.007$ ). In the high-dose statin cohorts, ezetimibe plus statin-80 reduced LDL-C by an additional 20.5% ( $P=0.0001$ ) versus statin-80. Similar significant reductions in LDL-C concentrations were observed for patients with genotype-confirmed HoFH (n=35). Ezetimibe was safe and well tolerated.

**Conclusions**—Ezetimibe coadministered with atorvastatin or simvastatin in patients with HoFH produced clinically important LDL-C reductions compared with best current therapy. Ezetimibe provides a new, complementary pharmacological approach for this high-risk population. (*Circulation*. 2002;105:2469-2475.)

**Key Words:** hypercholesterolemia ■ lipoproteins ■ cholesterol ■ lipids ■ statins

Homozygous familial hypercholesterolemia (HoFH) is an autosomal-dominant inherited disorder, usually caused by mutations at the gene locus responsible for encoding the LDL receptor, which results in defective LDL catabolism, markedly increased plasma concentrations of LDL cholesterol (LDL-C), premature atherosclerosis, and myocardial infarction.<sup>1-3</sup> Although the incidence of the homozygous disease is ≈1 per million, the incidence of the heterozygous condition is ≈1 per 500.<sup>4</sup> HoFH patients have a lower response rate to available pharmacological therapies aimed at lowering LDL-C than patients with heterozygous familial hypercholesterolemia.<sup>10</sup> The medical management of HoFH is challenging because LDL-C levels remain high in most patients despite aggressive use of dietary maneuvers, 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors (statins), bile acid sequestrants, niacin, fibric

acid derivatives, or combination therapy. LDL apheresis offers promise as a treatment for the disorder<sup>10,11</sup>; however, it is time consuming and not available to many patients. Other aggressive therapeutic options include portacaval shunting and liver transplantation.<sup>10,12</sup>

Ezetimibe is the first of a new class of cholesterol absorption inhibitors that potently inhibits dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins.<sup>13-15</sup> Ezetimibe is absorbed rapidly, extensively conjugated to glucuronide in the intestine, and circulated enterohepatically.<sup>14,16,17</sup> In clinical studies of patients with primary hypercholesterolemia, ezetimibe at 10 mg/d significantly decreased LDL-C by ≈20% after 12 weeks of therapy and had a safety profile similar to placebo.<sup>17-20</sup> Additionally,

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\*The Writing Committee members and the Ezetimibe Study Group members are listed in the Appendix.

Drs Gagné, Gaudet, and Bruckert have either served as consultants for or received honoraria from Schering-Plough Research Institute and Merck/Schering-Plough Pharmaceuticals, and the other Writing Group members are employees of the Schering-Plough Research Institute.

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coadministration of ezetimibe with simvastatin or atorvastatin produced incremental LDL-C reductions and favorably affected total cholesterol, HDL cholesterol (HDL-C), and triglyceride levels.<sup>17,19,21-23</sup>

Because current pharmacological therapy of patients with HoFH fails to sufficiently reduce LDL-C concentrations, the present randomized, double-blind study evaluated the efficacy, safety, and tolerability of ezetimibe as an adjunct to diet and statins with or without LDL apheresis.

## Methods

Adults and children (at least 12 years old or body weight  $\geq 40$  kg) with HoFH were eligible for study. HoFH was determined by genetic testing confirming 2 mutated alleles at the LDL receptor locus or by clinical criteria,<sup>24</sup> which included a history of LDL-C  $\geq 220$  mg/dL (5.69 mmol/L) while receiving maximally tolerated lipid-lowering therapy with  $<15\%$  response; LDL-C above the 90th percentile in  $\geq 2$  first-degree relatives; and the presence of tendinous xanthomas and/or manifestations of premature coronary heart disease or corneal arcus (no patient was included solely on the basis of this characteristic). To account for the effects of LDL apheresis in patients receiving this modality, levels of plasma LDL-C (calculated using the Friedewald equation<sup>25</sup>)  $\geq 100$  mg/dL (2.59 mmol/L) and triglycerides  $\leq 350$  mg/dL (3.95 mmol/L) while receiving atorvastatin or simvastatin 40 mg/d were required, with a stable LDL apheresis regimen for  $\geq 8$  weeks. Adherence to the National Cholesterol Education Program<sup>26</sup> Step I or stricter diet was also required. Exclusion criteria included significant liver disease or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) determinations  $>2$  times the upper limit of normal, significant renal disease, unstable coronary syndromes or advanced congestive heart failure, or ongoing treatment with fibrin acid derivatives (other lipid-lowering agents could be continued as long as the dose was stable).

## Study Design

This randomized, double-blind, parallel-group study was approved by the independent review board at each study center, and all patients and parents of child participants gave written informed consent. The study protocol included 2 treatment phases. A 6- to 14-week open-label, nonrandomized statin (atorvastatin or simvastatin 40 mg/d; the 2 statins the US Food and Drug Administration has approved for this indication) lead-in phase (statin-40) was followed by a 12-week study phase during which qualifying patients were randomized to receive 1 of 3 once-daily double-blind treatments: statin 80 mg (statin-80), ezetimibe 10 mg plus statin 40 mg (ezetimibe plus statin-40), or ezetimibe 10 mg plus statin 80 mg (ezetimibe plus statin-80). Patients continued on the prescribed diet and same statin as received during the open-label phase, although the randomly assigned statin dose and the addition of ezetimibe or placebo were blinded. Visits occurred at 2- to 4-week intervals, during which lipid and safety variables were measured. In patients receiving LDL apheresis (usually performed every 2 weeks), lipid concentrations were measured immediately before the apheresis procedure throughout the study.

## Assessment of Efficacy

The primary efficacy variable was the percentage change from baseline while receiving either open-label atorvastatin or simvastatin 40 mg/d (statin-40) to study end point in the plasma concentration of directly measured LDL-C, determined with the use of a standardized ultracentrifugation/precipitation procedure. The intention-to-treat primary analysis compared the statin-80 group with the group receiving ezetimibe plus either 40 or 80 mg statin (ezetimibe plus statin-40/80). The cohorts of all patients receiving simvastatin or atorvastatin 80 mg (high-dose statin group) were analyzed as a prespecified subgroup. Secondary efficacy end points included the percentage of change from baseline to end point determined for

calculated<sup>25</sup> LDL, HDL, and total cholesterol; triglycerides; subfractions HDL<sub>2</sub> and HDL<sub>3</sub> cholesterol; apolipoproteins A-I and B; lipoprotein(a); and the ratios of LDL-C:HDL-C and total cholesterol:HDL-C. Central laboratories (Medical Research Laboratories, Highland Heights, Ky, or Clinical Research Laboratories, Zaventem, Belgium) performed all laboratory tests. Measurements were made before randomization and 2, 4, 8, and 12 weeks after randomization.

## Assessment of LDL Receptor Gene Mutation

Twenty-six patients had previous genotype confirmation, by local laboratories, of either true homozygote (same mutations on each allele) or compound heterozygote (different mutations on each allele); participants without previous genotype determinations were tested using standardized techniques by a central laboratory (Dr J. Defesche, Amsterdam, the Netherlands). Genotypic determinations were based on established methodologies of DNA isolation and polymerase chain reaction gene amplification described previously to confirm specific mutations for the 18 exons of the LDL receptor gene,<sup>27-31</sup> and to screen for the R3500Q mutation of the apolipoprotein B gene.<sup>31,32</sup> Individual reported base pair changes or deletions in the LDL receptor gene were compared against published DNA sequences, allele designations, and mutational classes of the LDL receptor gene.<sup>33-35</sup>

## Assessment of Safety

Safety and tolerability were assessed by clinical review of all safety parameters, including adverse events, laboratory test results (including frequent liver function tests and creatine kinase levels), and physical examinations.

## Statistical Analysis

The primary analysis was performed using an ANOVA model that extracted sources of variation due to treatment (the addition of ezetimibe 10 mg) and statin. The reported mean lipid concentrations are the least-square mean values determined by ANOVA. Categorical data were examined between treatment groups using a  $\chi^2$  analysis.

Data are expressed as least-square mean  $\pm$  SEM; *P* values  $<0.05$  were considered statistically significant.

## Results

### Patient Population

A total of 50 patients (21 males and 29 females) received randomized treatment between May 3, 2000, and May 25, 2001. Five additional patients were screened but not enrolled because of patient preference ( $n=3$ ), an exclusion criterion ( $n=1$ ), or an adverse event ( $n=1$ ). Sixteen patients were randomized to ezetimibe 10 mg/d plus statin-40, 17 to ezetimibe plus statin-80, and 17 to statin-80. Thus, 33 patients received ezetimibe coadministered with statin at either 40 or 80 mg/d for the primary end-point comparison versus statin-80. More randomized patients received atorvastatin ( $n=36$ ) than simvastatin ( $n=14$ ) because the former agent was more commonly used during the open-label nonrandomized phase.

Table 1 summarizes the demographic characteristics, which were similar between the 2 treatment groups. Genotyping revealed that 35 patients had mutations in both LDL receptor alleles (19 true homozygotes and 16 compound heterozygotes). Despite the presence of the HoFH clinical phenotype, a genotype-confirmed mutation was identified in one allele in 7 patients and in neither allele in 5 patients (one patient had a mutation at the apolipoprotein B gene locus in addition to the LDL receptor locus; full genotyping was not performed in 3 patients). Attempts were not made to determine the presence of mutations resulting in the HoFH

TABLE 1. Baseline Characteristics of Patients Randomized to Treatment

Characteristic*	Statin-80 (n=17)	Ezetimibe Plus Statin-40/80 (n=33)
Age, y (median)	33±4 (30)	32±3 (31)
Age ≥18 y, n (%)	15 (88)	28 (85)
Female, n (%)	12 (71)	17 (52)
White, n (%)	16 (94)	29 (88)
Body mass index, kg/m <sup>2</sup>	25±1	26±1
Diagnosis of HoFH at study entry, n (%)		
Genotype-confirmed diagnosis	11 (65)	15 (45)
Clinical phenotype†	6 (35)	18 (55)
Tendinous xanthomas	15 (88)	28 (85)
Premature corneal arcus	8 (47)	20 (61)
Cutaneous xanthomas	0	2 (6)
Premature coronary heart disease	7 (41)	15 (45)
Concomitant lipid-lowering treatments, n (%)		
LDL apheresis	8 (47)	17 (52)
Bile acid sequestrants	2 (12)	6 (18)
Nicotinic acid	1 (6)	1 (3)
Lipid concentrations, mg/dL‡		
Direct LDL-C§	339±29	313±22
Calculated LDL-C§	341±29	316±22
Total cholesterol§	404±30	379±22
Apolipoprotein B	269±19	253±14
HDL-C§	43±3	42±2
HDL <sub>2</sub> cholesterol§	16±1	17±1
HDL <sub>3</sub> cholesterol§	27±2	26±1
Apolipoprotein A-	124±6	120±4
Direct LDL-C:HDL-C ratio	8±1	8±1
Total cholesterol:HDL-C ratio	10±1	10±1
Triglycerides¶	102±14	110±10
Lipoprotein(a)#	33±5	29±4

\*Noncategorical data are presented as least-square mean±SEM.

†Clinical criteria are defined in Methods.

‡Determined while receiving simvastatin or atorvastatin 40 mg/d in addition to other lipid-lowering therapies (eg, LDL apheresis).

§To convert values to mmol/L, multiply by 0.02586.

||To convert values to g/L, multiply by 0.01.

¶To convert values to mmol/L, multiply by 0.01129.

#To convert values to mmol/L, multiply by 10.

phenotype that did not affect the LDL receptor or apolipoprotein B gene locus.<sup>5-7</sup> Fifty percent of the patients were undergoing concomitant LDL apheresis.

### Efficacy

Treatment with ezetimibe plus statin-40/80 resulted in greater direct LDL-C reduction from baseline (statin-40) to end point compared with statin-80 (-20.7% versus -6.7%,  $P=0.007$ ;  $313\pm22$  to  $247\pm21$  mg/dL [ $8.10\pm0.55$  to  $6.39\pm0.55$  mmol/L] versus  $339\pm29$  to  $319\pm28$  mg/dL [ $8.76\pm0.74$  to  $8.24\pm0.73$  mmol/L]). The LDL-C-lowering effect of ezetimibe plus statin-40/80 was observed as early as 2 weeks after ezetimibe initiation and persisted throughout

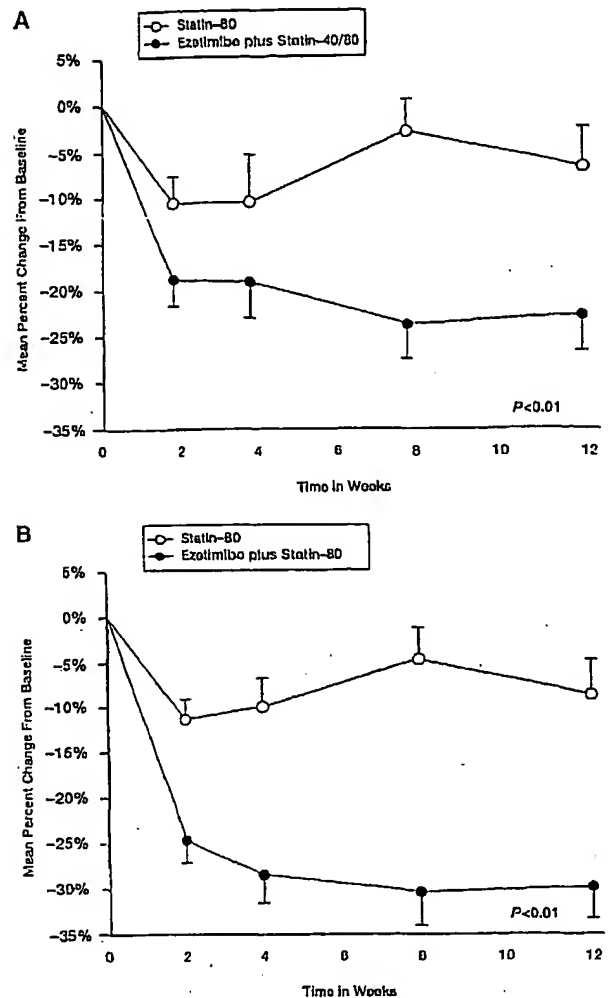
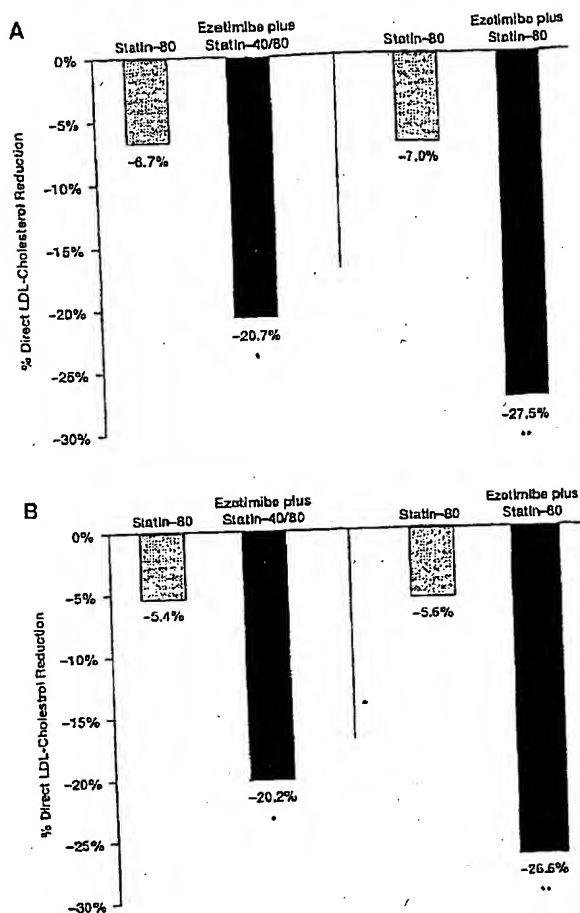


Figure 1. Mean percentage reduction in LDL-C over time for patients with homozygous familial hypercholesterolemia receiving ezetimibe plus statin-40/80 compared with patients receiving statin-80. A, Mean percentage reduction in LDL-C over time for patients receiving statin-80 versus ezetimibe plus statin-40/80. B, Mean percentage reduction in LDL-C over time for patients receiving statin-80 versus ezetimibe plus statin-80.

the 12-week study (Figure 1A). A reduction of  $\geq 15\%$  in direct LDL-C levels was observed in only 18% of patients in the statin-80 group, compared with 58% of patients receiving ezetimibe plus statin-40/80 ( $P=0.001$ ). The addition of ezetimibe to the 16 patients receiving statin-40 resulted in an additional LDL-C reduction of  $-12.8\pm5.0\%$ . The greater effect of ezetimibe plus statin-40/80 in reducing LDL-C was consistent among subgroups, regardless of sex, age, race, or baseline total or LDL-C concentrations. Although patients were not stratified on the basis of concomitant LDL apheresis, similar reductions in LDL-C were observed in patients with or without LDL apheresis. There were no apparent differences in LDL-C lowering by ezetimibe between patients receiving either atorvastatin or simvastatin.

Comparison of the high-dose statin groups provides the best estimate of LDL-C lowering specifically attributable to ezetimibe because the statin dose was increased from 40 to 80



**Figure 2.** Mean percentage reduction in LDL-C at study end point for patients with homozygous familial hypercholesterolemia receiving ezetimibe plus statin-40/80 compared with patients receiving statin-80. **A**, Percentage reduction in LDL-C at study end point in the entire study cohort. Left bars, Ezetimibe plus statin-40/80 ( $n=33$ ) versus statin-80 ( $n=17$ ). Right bars, Ezetimibe plus statin-80 ( $n=17$ ) versus statin-80 ( $n=17$ ). Treatment effects between groups were statistically significant for coadministration therapy with ezetimibe plus statin-40/80 versus statin-80 monotherapy ( $P=0.007$ ), and ezetimibe plus statin-80 versus statin-80 monotherapy ( $P=0.0001$ ). Values calculated as least-square mean percentage change from baseline (2-way ANOVA with effects for treatment and statin). \* $P=0.007$ ; \*\* $P=0.0001$ . **B**, Percentage reduction in LDL-C at study end point in patients with genotype-confirmed homozygous familial hypercholesterolemia. Left bars, Ezetimibe plus statin-40/80 ( $n=20$ ) versus statin-80 ( $n=15$ ). Right bars, Ezetimibe plus statin-80 ( $n=9$ ) versus statin-80 ( $n=15$ ). Treatment effects between groups were statistically significant for coadministration therapy with ezetimibe plus statin-40/80 versus statin-80 monotherapy ( $P=0.02$ ), and ezetimibe plus statin-80 versus statin-80 monotherapy ( $P<0.01$ ). Values calculated as least-square mean percentage change from baseline (2-way ANOVA with effects for treatment and statin). \* $P=0.02$ ; \*\* $P<0.01$ .

mg (with or without addition of ezetimibe) in both groups. This analysis demonstrated that ezetimibe plus statin-80 significantly reduced LDL-C compared with statin-80 alone ( $-27.5\%$  versus  $-7.0\%$ ,  $P=0.0001$ ;  $273\pm 20$  to  $196\pm 21$  mg/dL [ $7.06\pm 0.52$  to  $5.07\pm 0.54$  mmol/L] versus  $341\pm 20$  to

$319\pm 21$  mg/dL [ $8.87\pm 0.52$  to  $8.25\pm 0.54$  mmol/L]; Figures 1B and 2A). Because the baseline LDL-C level in the statin-80 group was significantly higher compared with the ezetimibe plus statin-80 group, the effect of ezetimibe was reexamined using an analysis of covariance incorporating baseline LDL-C values as covariates. This examination confirmed the above findings. Seventy-six percent of patients in the ezetimibe plus statin-80 group had a  $\geq 15\%$  reduction in direct LDL-C compared with 18% of patients in the statin-80 group ( $P<0.001$ ).

Similar significant reductions in direct LDL-C concentrations were observed in the 35 genotype-confirmed HoFH patients (Figure 2B). Ezetimibe plus statin-40/80 ( $n=20$ ) administration reduced LDL-C  $-20.2\%$  ( $344\pm 30$  to  $269\pm 29$  mg/dL [ $8.90\pm 0.78$  to  $6.96\pm 0.75$  mmol/L]) compared with  $-5.4\%$  ( $333\pm 30$  to  $316\pm 30$  mg/dL [ $8.61\pm 0.78$  to  $8.17\pm 0.78$  mmol/L],  $P=0.02$ ) in the statin-80 group ( $n=15$ ). Comparison of the genotype-confirmed HoFH patients in the high-dose statin groups demonstrated that ezetimibe plus statin-80 significantly reduced LDL-C compared with statin-80 ( $-26.6\pm 4.7\%$  versus  $-5.6\pm 3.3\%$ ,  $P<0.01$ ). The LDL-C changes in true homozygotes receiving ezetimibe plus statin-40/80 ( $-20.7\pm 7.4\%$ ) were similar to those in compound heterozygotes ( $-19.6\pm 5.0\%$ ).

For total cholesterol concentrations, the difference in mean percentage change from baseline to end point between the ezetimibe plus statin-40/80 and the statin-80 groups ( $-18.7\%$  versus  $-5.3\%$ ) was statistically significant ( $P<0.01$ ). There were no significant differences between the study groups in effect on mean HDL-C, triglycerides, or apolipoproteins B or A-I concentrations (Table 2). Because of wide inpatient variability in the effects on mean apolipoprotein B, analysis of the median percentage change was performed, showing a reduction with ezetimibe ( $-16\%$  versus  $-4.1\%$ ,  $P=0.06$ , ezetimibe plus statin-40/80 versus statin-80;  $-17.9\%$  versus  $-4.1\%$ ,  $P=0.01$ , ezetimibe plus statin-80 versus statin-80). The mean percentage change in LDL-C:HDL-C ratio was not significantly different in the primary analysis groups but was reduced in the high-dose statin group ( $-23.6\%$  versus  $-10.0\%$ ,  $P<0.05$ , ezetimibe plus statin-80 versus statin-80).

### Safety Profile

The safety results and most commonly reported adverse events are reported in Table 3. There were no clinically meaningful differences between treatment groups. Forty-eight patients (96%) completed the double-blind treatment period, with only 2 patients discontinuing treatment early because of adverse events. One patient in the ezetimibe plus statin-40 mg group discontinued the study drug 9 weeks after randomization because of epigastric pain secondary to an intrahepatic echinococcal cyst (with increased liver transaminases) and ischemic chest pain. A second patient in the ezetimibe plus statin-80 group was discontinued from the study 1 week after randomization when it was noted that his baseline prerandomization serum ALT and AST levels were  $>3$  times the upper limit of normal, in violation of the protocol exclusion criteria.

Analyses of additional measures of safety (laboratory results, electrocardiograms, and cardiopulmonary examina-

TABLE 2. Changes in Plasma Concentrations of Lipid-Related Variables From Baseline to End Point

Variable	Statin-80 (n=17)*		Ezetimibe Plus Statin-40/80 (n=33)*		P
	Absolute Change (mg/dL)	% Change	Absolute Change (mg/dL)	% Change	
Direct LDL-C	-20.2	-6.7	-66.0	-20.7	0.00†
Calculated LDL-C	-19.9	-6.6	-68.0	-21.4	<0.01
Total cholesterol	-19.3	-5.3	-72.7	-18.7	<0.01
Apolipoprotein B	-10.1	-1.9	-25.5	-3.7	0.87
Median % change	—	-4.1	—	-16.0	0.06
HDL-C	1.8	4.4	-1.2	-2.8	0.09
HDL <sub>2</sub> cholesterol	1.8	7.8	0.2	8.6	0.96
HDL <sub>3</sub> cholesterol	0.1	2.2	-1.3	-2.8	0.35
Apolipoprotein A-I	1.6	0.9	-0.9	-0.8	0.63
Direct LDL-C:HDL-C ratio	-0.9	-10.1	-1.2	-17.0	0.30
Total cholesterol:HDL-C ratio	-0.9	-8.8	-1.3	-15.2	0.27
Triglycerides	-5.7	-5.8	-17.3	-10.8	0.54
Lipoprotein(a)	-0.5	21.6	-0.8	7.0	0.40

\*Not every patient had an end-of-treatment measurement for every variable; the number of patients within groups ranged from 16 to 17 (statin-80) and from 29 to 33 (ezetimibe plus statin-40/80).

tions) revealed no differences between the treatment groups. One patient in the statin-80 group and one patient in the ezetimibe plus statin-40/80 group had asymptomatic single transient increases in serum ALT and/or AST >3 times the upper limit of normal. There were no clinically significant increases in creatine kinase concentrations or episodes of myopathy or rhabdomyolysis.

TABLE 3. Safety Results for Patients Randomized to Treatment

	Statin-80 (n=17)	Ezetimibe Plus Statin-40/80 (n=33)
Adverse event*	11 (65)	24 (73)
Headache	3 (18)	4 (12)
Pharyngitis	2 (12)	3 (9)
Upper respiratory tract infection	0	4 (12)
Nausea	2 (12)	1 (3)
Chest pain	2 (12)	1 (3)
Discontinuation due to adverse event	0	2 (6)‡
Increased liver function test $\geq 3 \times \text{ULN}$		
ALT and/or AST†	0	2 (6)‡
Total bilirubin	0	0
Alkaline phosphatase	0	1 (3)
Creatine phosphokinase $\geq 5 \times \text{ULN}$	0	0

Values are n (%). ULN indicates upper limit of normal.

\*Incidence  $\geq 10\%$  of patients in either group.

†Two consecutive determinations.

‡One patient with ALT and AST  $>3 \times \text{ULN}$  at baseline is included.

## Discussion

This randomized, double-blind study of 50 patients with HoFH represents the largest reported controlled study of any therapeutic intervention in individuals with this disorder. This study demonstrates clinically significant further reductions of at least 14.0% to 20.5% in LDL-C when ezetimibe was coadministered with a moderate (40 mg) or maximal (80 mg) dose of statin therapy compared with maximal therapy with statins alone. The importance of the present findings are highlighted by the well-known limitations of pharmacological therapy (including high-dose statin therapy) in reducing LDL-C in patients with HoFH as compared with other types of hypercholesterolemia.<sup>10</sup> On the basis of the current results and similar LDL-C reductions in primary hypercholesterolemia,<sup>17-22</sup> it would be anticipated that ezetimibe would exert comparable actions in other forms of severe hypercholesterolemia. The effect of statins in HoFH seems to be significantly limited by the inability of these patients to effectively upregulate the LDL receptor,<sup>10</sup> whereas the primary mechanism responsible for ezetimibe-induced LDL-C lowering, inhibition of cholesterol absorption at the intestinal brush border,<sup>13,14,23</sup> seems to be largely unaffected by the pathophysiological milieu of HoFH.

Ezetimibe plus statin-80 was almost 4 times more effective in reducing LDL-C than was doubling the statin dose from statin-40 to statin-80, the maximum recommended dose. LDL-C reductions were seen within 2 weeks, sustained throughout the study, and obtained in patients receiving dietary therapy and, in half of the patients, concomitant LDL apheresis. The incidence of adverse events and the safety profile of ezetimibe coadministered with statins were similar to patients receiving simvastatin or atorvastatin alone.

Ezetimibe coadministered with statins was not associated with clinical liver or muscle-related toxicity and seemed safe.

Given the international enrollment of patients with HoFH and range of genotypes, the results of this study should be widely applicable to patients with HoFH. Although the present study included patients with genotypically diagnosed HoFH and patients whose diagnosis was based on clinical criteria alone, the effects of ezetimibe on LDL-C concentrations in genotype-confirmed homozygous or compound heterozygous patients were significant and similar to the whole-study cohort. Including both populations of patients in the study parallels the clinical "real-world" setting in which many diagnosed patients are not genotyped. Twelve patients with phenotypic HoFH at study entry subsequently had their genotypes defined and were found not to have mutations affecting the gene locus on both alleles coding for the LDL receptor. Consistent with previous studies, the HoFH phenotype in these cases presumably reflected the consequences of other mutations in other genes.<sup>5-7</sup>

The present study had several limitations. First, the wide range of HoFH genotypes precluded examining different responses to ezetimibe as a function of specific LDL receptor gene mutations. Second, LDL apheresis was stabilized by study design, and the results of ezetimibe were consistent regardless of LDL apheresis. However, patients were not randomized to or stratified by LDL apheresis, and thus the beneficial effect of ezetimibe in patients with this procedure versus those without cannot be definitely determined. Finally, the 12-week study period necessitates a longer time period to assess improvement in clinical outcome and modification of other disease parameters (eg, xanthoma formation and regression of atherosclerosis).

### Conclusions

Ezetimibe coadministered with atorvastatin or simvastatin significantly reduced LDL-C concentrations and was safe and well tolerated in patients with HoFH. Ezetimibe provides a new pharmacological approach, complementary to statins, for the treatment of HoFH.

### Appendix

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#### The Ezetimibe Study Group

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